HFA-305

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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R. William Soller, Ph.D.
Senior Vice President and
Director of Science and Technology
Consumer Healthcare Products Association
1150 Connecticut Avenue, N.W.
Washington, D.C. 20036

Re: Docket No. 78N-036L
Comment No. CP19

Dear Dr. Soller:

Reference is made to your citizen petition dated November 10, 1994, which was filed under Docket No. 78N-036L in the Dockets Management Branch as Comment No. CP19. The petition requested that FDA include calcium polycarbophil as a Category I (safe and effective) bulk laxative ingredient in the final monograph for OTC laxative drug products. The petition included published references and other data to support the Category I status of calcium polycarbophil. The petition also stated that good cause exists for the FDA to reopen the laxative docket and amend the laxative monograph to include calcium polycarbophil prior to publication of the final monograph. You stated that this action was warranted because prior to September 1994, it appeared that FDA considered calcium polycarbophil to be a Category I laxative ingredient, based on its classification in FDA's OTC Drug Review Ingredient Status Report and in a summary table in the OTC laxative tentative final monograph (50 FR 2124 at 2149). However, the September 1994 Ingredient Status Report changed the status of calcium polycarbophil to "N/A," meaning that the ingredient was either not classified by the Panel or was not included in the indicated document. You further stated that no explanation was provided for this action, and, thus, the issue of classification should be reopened.

The Division of OTC Drug Products notes that the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel) reviewed polycarbophil, but not calcium polycarbophil as an laxative active ingredient (40 FR 12902 at 12906). Calcium polycarbophil was inadvertently listed as a Category I laxative ingredient in a chart in the preamble to the tentative final monograph for OTC laxative drug products. However, the tentative final monograph did not include calcium polycarbophil as a laxative active ingredient in § 334.10 of the proposed monograph. Thus, the "N/A" listing of calcium polycarbophil in the 1994 Ingredient Status Report is correct.

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However, the Division of OTC Drug Products has reviewed the published references and other information submitted in CP19 and concludes that the data support the Category I status for calcium polycarbophil as an OTC bulk laxative drug ingredient.

We have the following comments.

Tisdale (Ref. 1), in a parallel, double-blind, multicenter study, compared two doses of calcium polycarbophil in 339 subjects with irritable bowel syndrome (IBS). Subjects were randomized to receive either 3 grams (g) per day, 6 g per day of calcium polycarbophil or placebo. The study was of 3-weeks duration, and subjects were evaluated at baseline and after 1 and 3 weeks of therapy. The investigators stated that significant drug-placebo differences were not seen at the 1-week follow-up, but required 3 weeks of therapy to become manifest. Although the study was directed at subjects with IBS only, a subgroup analysis on the data taken from the subjects with predominately the constipation component of IBS showed no statistical significance except for the 6 g per dose vs. placebo using a one-tailed test. The investigators concluded that the results showed that these subjects had significant improvement in their symptoms while on treatment. However, after 6 weeks, 63 percent of subjects were still taking a median dosage of 2 g per day for symptomatic relief. It is not known whether patients with predominately the constipation of IBS still had periodic diarrhea. Because the parameters of efficacy used in the study were the number of subjects with abdominal pain or bowel trouble rather than more objective parameters, such as increased frequency of bowel movement, this study is not adequate to demonstrate the efficacy of calcium polycarbophil as an OTC laxative.

In a study by Toskes et al. (Ref. 2), twenty-three subjects were enrolled in a placebo controlled, double-blinded, crossover study to evaluate the efficacy of calcium polycarbophil in relieving the symptoms of IBS. Subjects were assigned to receive either calcium polycarbophil tablets at a dosage of 6 g per day in four divided doses or matching placebo tablets for a period of 12 weeks. Subjects were then crossed-over to receive the alternate treatment for 12 weeks. Subject assessments of stool frequency, consistency, and ease of passage and subjective assessments of nausea, bloating, and abdominal pain were recorded daily. Symptom improvement of the subjective symptoms and ease of stool passage were compared between the two treatments. There were no statistical differences between the two groups for the first three symptoms. However, a significant difference was found in favor of calcium polycarbophil for ease of stool passage ($p=0.05$). The authors concluded that, overall, there was a higher subject preference of calcium polycarbophil over the placebo.

Although the studies (Refs. 1 and 2) suggest that calcium polycarbophil may cause some improvement in symptoms of constipation, subjects with IBS represent a unique patient population, and these studies cannot be used to determine the laxative effects of calcium polycarbophil in the general population.

In the other studies that were submitted in support of the efficacy of calcium polycarbophil, psyllium was used as the active control drug (Refs. 3 through 7). Although placebo controlled studies are preferable, these studies showed comparable efficacy with psyllium. The efficacy of psyllium as a laxative was previously discussed in the advance notice of proposed rulemaking (40 FR 12902 at 12908 and 12940). In that document, the Panel recommended that psyllium be generally recognized as safe and effective and the agency concurred in the tentative final monograph for OTC laxative drug products (50 FR 2124 at 2152 and 51 FR 35136-7). In addition to the studies previously reviewed by the Panel, other studies, such as the Fenn et al. study (Ref. 8), a single-blind, multi center, parallel-designed (functional constipation) and the small double-blind Thomas-Ridocci et al. study (Ref. 9), supports the superiority of psyllium-type laxatives over placebo. Thus, we accept psyllium as an active control in the submitted calcium polycarbophil studies.

Two selective population studies by Bass, Clark, and doPico (Ref. 3) and by Chokhavatia, Phipps, and Anuras (Ref. 4) support the comparability of calcium polycarbophil and psyllium in the OTC setting for the symptomatic relief of idiopathic constipation. Both were open-label, crossover studies in which subjects were enrolled if they had experienced significant pre-existing symptoms of constipation requiring prior treatment with any laxatives. Subjects were randomized to treatment with either calcium polycarbophil or psyllium. The maximum daily dosage of calcium polycarbophil permitted was 4 g. No dosage was given for the active control (psyllium). The three parameters evaluated in these studies were stool frequency, stool consistency on a 4-point scale, and strain on bowel movement on a 3-point scale. At the end of the study, subjects rated their preference for either psyllium or calcium polycarbophil. In the Bass, Clark, and doPico study (Ref. 3), there was no significant difference in the two groups for all parameters studied. The Chokhavatia, Phipps, and Anuras study (Ref. 4) showed no significant differences between the two groups for stool consistency and bowel strain. Thus, although comparison to baseline could not be assessed directly, the subjects experienced similar relief of their symptoms in each treatment arm reporting, on average, 8 stools per week.

In a 17-day unblinded two-phase parallel dose-response study by Hamilton et al. (Ref. 5), sixty subjects with chronic constipation were randomized into four groups (number per group not given). Subjects received placebo for the first 7 days, followed by either 1 g, 2 g, or 4 g of calcium polycarbophil for 10 days. The fourth group received psyllium mucilloid, an active control. The reported results indicated statistically significant (ANCHOVA, $p<0.05$, one sided test) differences in stool frequency and weights from a placebo tablet treatment run-in baseline (7 days) for both calcium polycarbophil and for psyllium mucilloid. The mean stool frequencies increased from documented constipation on placebo to greater than 3 stools per week (constipation alleviated) in all active treatment arms. Although some improvement was shown in this study, the results were presented only as a brief discussion with four bar graphs. Further, it is not clear whether the medications were given as a single daily dose or divided doses. The few parameters where differences were observed were for the 1 and 4 g dose only. The analysis seemed to employ the mean of all subjects in each group, but the standard deviation was not

provided. The results of the above studies indicate reasonable statistical evidence that stool frequency is improved by calcium polycarbophil.

In a brief report of a study by Mamtani et al. (Ref. 6), thirty-two mentally alert elderly subjects were randomized to receive 2 tablets of a product containing calcium polycarbophil or 1 teaspoonful of a psyllium-containing product in 8 ounces of water twice daily for 3 weeks and then crossed-over to the other treatment for another 3 weeks. The study evaluated three parameters, i.e., stool frequency, consistency, and strain on bowel movement. The results of the study indicated no statistical differences between the two treatment groups. However, more subjects preferred calcium polycarbophil over psyllium. The authors suggested that this preference was due to ease of administration (tablet vs. suspension) and fewer side effects of bloating and flatulence.

In a blind, crossover, randomized study by Garcia and Mirabent (Ref. 7), forty subjects diagnosed with constipation were divided into two groups (Group A and Group B) of 20 each. Before starting treatment, there was a 7-day washout period for all subjects. Subjects in group A were then given calcium polycarbophil for 7 days (A1) followed by 7 days of psyllium (A2). Subjects in Group B were given psyllium (B1) followed by 7 days of treatment with calcium polycarbophil (B2). Subjects were treated twice a day either with 1 g of calcium polycarbophil or 7 g of psyllium. All subjects completed the study. The authors stated that the parameters of effectiveness were "better or improved." Improvement of constipation was evaluated daily on a scale of zero to ten (scale parameters not given). No other objective parameters of effectiveness were given. At the end of the first 7 days there were no statistical differences between the calcium polycarbophil (A1) and the psyllium group (B1) ($p<0.2$). However, at the end of 14 days, the authors reported that results in the calcium polycarbophil group (B2) were superior ($p>0.05$) and were also superior to the A1, B1, and the A2 groups. The authors concluded that calcium polycarbophil was better in the long term than psyllium, which infers that a period of adaptation to new intestinal habits is required before the regulatory effects of laxatives that increase the feces mass are manifested completely. Most of the subjects (70 percent) preferred calcium polycarbophil to psyllium. There are several problems with the basic design of this study. For example, although there was a 7-day washout period before the start of the study, no washout period was provided before subjects were crossed over to the next treatment. Thus, a carry over effect of the previous treatment cannot be ignored. The methods of randomization and statistical analysis were not provided. The scale used to assess the "improvement" values was too broad and subjective depending upon a subject's individual definition. Also, because of the length of time it took for the effect of the drug to manifest itself, it appears that the calcium polycarbophil dose was inadequate. Thus, this study cannot be adequately evaluated.

Thirty subjects with constipation participated in an 8-week, single-blind, crossover clinical study by Gizzi et al. (Ref. 10). Subjects were given two tablets of calcium polycarbophil containing 500 milligrams (mg) of polycarbophil three times a day for four weeks. Subjects were then crossed over to placebo (not identified) for four weeks. Subjects maintained a daily diary

throughout treatment. The principal parameters of effectiveness were frequency, exertion of bowel movement, and stool consistency. The authors reported that the data were collected and analyzed by descriptive statistical analysis methods. Three dropouts were excluded from the analysis. The reported results, by bar graphs only, indicate that during the administration of the drug, evacuations accompanied by excessive exertion were reduced and evacuations not accompanied by exertions were increased. The number of bowel movements with a hard stool was decreased while the number of stools with soft consistency increased. The authors reported that according to clinical opinion, efficacy was optimal in 78 percent of subjects and good in 22 percent. Tolerability, both gastrointestinal and systemic, was optimal in 100 percent of the subjects. Analysis of hematochemical parameters showed only a mild increase in calcemia, accompanied by a parallel rise in calciuria. No other adverse reactions were seen due to the drug. Although the study suggests that calcium polycarbophil may be effective for the relief of constipation, the lack of detailed data makes it difficult to adequately evaluate the study.

In a 5-week, open, outpatient, pilot study by Mondardini et al. (Ref. 11), seventeen severely constipated subjects were given two 625 mg calcium polycarbophil tablets (500 mg polycarbophil equivalent) three times a day. Three subjects did not complete the study and four subjects had false constipation. All seven were excluded. The study consisted of two weeks of observation followed by three weeks of treatment. The ten remaining subjects served as their own control. During the observation period, subjects were allowed free use of their regular laxatives. Subjects kept a daily diary in which the daily number of bowel movements, the straining score (none =1, moderate = 2, excessive = 3), and the stool consistency score (very hard = 4, moderately hard = 3, soft = 2, liquid = 1) were recorded. Ten subjects completed treatment. The parameters of effectiveness analyzed were average number of bowel movements per week; average stool consistency; straining per bowel movement; and the results prior to, and during the therapy were compared. The data were analyzed statistically with the t-test for paired data. The average number of bowel movements increased from 3 ±0.8 (range 1.5 to 4) to a weekly evacuation average of 5 ±2 (range 1.5 to 7; $t = 3.6$; $p<0.005$). The effort of passing stools was shown to be moderate (average straining score assigned = 2.2). The consistency of stool was not statistically significant, $t = 1.63$. Because this was an unblinded outpatient study, the potential for investigator and subject bias is of concern. Compliance to treatment was not assured by the investigators. Further, free use of laxatives during the observation period did not provide a true baseline upon which to compare treatment to placebo. Also, carry-over effects cannot be ruled out. Moreover, the study sample size was small and it is difficult to extrapolate the findings to the general population.

The efficacy of calcium polycarbophil was evaluated in a single-blind, crossover study by Pallotta et al. (Ref. 12). Subjects with chronic non-organic constipation were given either 1.25 g of calcium polycarbophil three times a day or placebo for 4 weeks then crossed over to the other treatment for 4 weeks. Parameters assessed were strength of evacuation force and consistency of feces. The authors reported that calcium polycarbophil caused a reduction in the difficulty of evacuation and an emission of feces of a softer consistency. The study data were analyzed via descriptive statistical analyses (SPSS, PC) and by appropriate statistical tests (χ^2 analysis of variance). However, because no raw data were given and the results per week were averaged over the four-week period and expressed in percent evacuations or consistency only, the findings

of this study cannot be evaluated.

Although the above studies contained some methodologic faults, there is reasonable statistical evidence that demonstrates the comparability of psyllium, a Category I bulk laxative active drug ingredient, and calcium polycarbophil, and to show the superiority of calcium polycarbophil over placebo in the treatment of the symptoms of constipation.

As referenced in your petition and in the tentative final monograph for OTC antidiarrheal drug products (51 FR 16138 at 16141), calcium polycarbophil is a salt of the active ingredient polycarbophil, and is converted to polycarbophil in the stomach. In the stomach, the calcium salt is converted to acidic polycarbophil when the calcium is replaced by hydrogen ions of the stomach acid. Because the calcium ion does not alter either the chemical or pharmacological effect of polycarbophil, calcium polycarbophil can be considered to be therapeutically identical to polycarbophil. Reevaluation of data submitted to the Panel (40 FR 12902 at 12908) and data submitted in your petition (Refs. 13 and 14), indicated that the data support a daily dosage of 4 g of polycarbophil for adults and children 12 years of age and over, 2 g for children 6 to under 12, and 1 g for children 2 to under 6. For children under 2 years of age, consult a doctor.

Based on the data evaluated, that calcium polycarbophil is gram equivalent to polycarbophil oral, (i.e., 625 mg of calcium polycarbophil is equivalent to 500 mg of polycarbophil), the Division intends to recommend that the final monograph include the following oral dosages for calcium polycarbophil: for adults and children 12 years of age and over: 5 g (equivalent to 4 g polycarbophil), for children 6 to under 12 years of age: 2.5 g daily, for children 2 to under 6 years of age: 1.25 g daily, and children under 2 years of age: consult doctor. The amended oral dosages for polycarbophil and calcium polycarbophil will be further discussed in the OTC laxative final monograph to be published in the near future.

The Division intends to recommend to the Commissioner that the agency respond to your petition by including polycarbophil and calcium polycarbophil in the final monograph for OTC laxative drug products, which will be published in a future issue of the Federal Register.

If you have any questions regarding the petition, please refer to the docket number above and submit all inquiries in triplicate, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely yours,

Linda M. Katz, M.D., M.P.H.
Deputy Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

References

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(4) Chokhavatia, S., T. Phipps, and S. Anuras, "Comparative Laxation of Calcium Polycarbophil with Psyllium Mucilloid in an Ambulatory Geriatric Population," Current Therapeutic Research, 44: 1013-1019, 1988.

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(13) Grossman, A. J., R. C. Batterman, and P. Lifer, "Polyacrylic Resin: Effective Hydrophilic Colloid for the Treatment of Constipation," Journal of the American Geriatric Society, 5:1876-192, 1957.

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M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/4/99

FROM: Director
Division of OTC Drug Evaluation, HFD-560

SUBJECT: Material for Docket No. 78N-0361

TO: Dockets Management Branch, HFA-305

[X] The attached material should be placed on public display under the above referenced Docket No.

[X] This material should be cross-referenced to Comment No. CP19.

Debra L. Bowen, M.D.

Attachment